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TITLE: Interrelationships of Prenatal and Postnatal Growth, Hormones, Diet and Breast Cancer

PRINCIPAL INVESTIGATOR: Maureen Sanderson, Ph.D.

CONTRACTING ORGANIZATION: University of South Carolina
Columbia, South Carolina 29208

REPORT DATE: June 2001

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*

The purpose of this Career Development Award was to expand Dr. Sanderson's current breast cancer research from the effect of intrauterine exposure to estrogen on breast cancer to the interrelationships of prenatal and postnatal growth, hormones, diet and breast cancer. Based on these interrelationships, we hypothesized that insulin resistance will be positively associated with breast cancer. Further, we hypothesized that genetic susceptibility, and adolescent/adult diet and physical activity will modify the effect of insulin resistance on breast cancer. Specific aims were: 1) to undergo intensive training in cancer biology, and nutritional, molecular and genetic epidemiology, 2) to obtain funding to conduct case-control studies of the insulin resistance-breast cancer relationship, and 3) to obtain funding to conduct a cohort study of the association between prenatal and postnatal growth and infant hormone levels.

To date, Dr. Sanderson has audited Pathology of Neoplasia, gained knowledge of analyses of dietary intake and anthropometric measurements, submitted an Idea Award to the Department of Defense to investigate insulin resistance and breast cancer, analyzed data from the Shanghai Breast Cancer Study, and participated in a childhood obesity work group at the University of South Carolina. Dr. Sanderson is transferring this Award to the University of Texas School of Public Health - Brownsville.

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Breast Cancer, Epidemiology/Biostatistics, Nutrition, Hormone Metabolism

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Table of Contents

Introduction

The purpose of this Career Development Award was to expand Dr. Sanderson's current breast cancer research from the effect of intrauterine exposure to estrogen on breast cancer to the interrelationships of prenatal and postnatal growth, hormones, diet and breast cancer. Based on these interrelationships, we hypothesized that insulin resistance would be positively associated with breast cancer. Further, we hypothesized that genetic susceptibility, and adolescent/adult diet and physical activity would modify the effect of insulin resistance on breast cancer. Specific aims were: 1) to undergo intensive training in cancer biology, and nutritional, molecular and genetic epidemiology, 2) to obtain funding to conduct case-control studies of the insulin resistance-breast cancer relationship, and 3) to obtain funding to conduct a cohort study of the association between prenatal and postnatal growth and infant hormone levels.

Body

I am in the process of submitting paperwork to revise my approved Statement of Work because Drs. Wei Zheng and Xiao-Ou Shu, two of my three mentors, left the University of South Carolina for Vanderbilt University in July 2000. In addition, I will be leaving the University of South Carolina for the University of Texas School of Public Health – Brownsville in August 2001. My mentors, Drs. Zheng, Shu and Elizabeth Mayer-Davis (University of South Carolina), have agreed to continue in those roles, and Dr. Rena S. McPherson from the University of Texas School of Public Health has agreed to be added as an on-site mentor.

Under my Statement of Work, I completed Task 1.a. by auditing Pathology of Neoplasia with Dr. Kim Creek at the University of South Carolina School of Medicine in Fall 2000 (Appendix A). I will modify Task 1.b. by auditing Nutritional Epidemiology with Dr. McPherson. I will modify Task 1.c. and Task 1.d. by working with Dr. McPherson to assess nutritional status and physical activity and to validate a food frequency questionnaire using studies based at the University of Texas School of Public Health. I partially completed Task 1.c. by gaining knowledge of analyses of dietary intake and anthropometric measurements; I co-authored the manuscript "Dietary exposures and oral precancerous lesions in Srikakulam District, Andhra Pradesh, India" (Appendix B) and presented the poster "Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population" (Appendix C) at the Society for Epidemiologic Research Meeting. The manuscript on the latter topic is in progress.

I partially completed Task 1.e. by submitting an Idea Award to the Department of Defense entitled "Prenatal and Postnatal Growth, Hormones, Diet and Breast Cancer" in June 2000 (Appendix D). The purpose of this ancillary study was to expand Dr. James Hebert's Department of Defense study "Quasi-Prospective Study of Breast Cancer and Diet" to collect, process and analyze blood for estradiol (E2), sex hormone-binding globulin (SHBG), insulin-like growth factor 1 (IGF1), insulin-like growth factor binding protein 3 (IGFBP3), insulin and glucose. The hypotheses were: 1) insulin resistance, defined as high levels of insulin and glucose or type 2 diabetes, would be positively associated with breast cancer, 2) the insulin resistance-breast cancer association would be mediated, in part, through abdominal obesity, E2, SHBG, IGF1, and IGFBP3, alone or in combination, and 3) the insulin resistance-breast cancer relation would be modified by birthweight, age at which adult height was achieved, diet, physical activity, and weight gain, alone or in combination. The grant received a score of 2.5, but was not

recommended for funding. The major strength of the grant was the exploration of several novel ideas regarding breast cancer risk, while the major limitation was its' case-control design. I will resubmit the grant from the University of Texas School of Public Health - Brownsville. I analyzed data from the Shanghai Breast Cancer Study and authored the article entitled "Abortion history and breast cancer risk: Results from the Shanghai Breast Cancer Study" (Appendix E).

I will modify Task 2.a. and Task 2.b. by auditing Molecular Epidemiology with Dr. Corinne Aragaki and Genetic Aspects of Epidemiology with Dr. Ranajit Chakraborty at the University of Texas School of Public Health. Task 2.c., Task 2.e. and Task 2.f. are pending, and Task 2.d. has not been funded and may need to be eliminated from the Statement of Work. I began work on Task 2.f. by participating in a childhood obesity work group at the University of South Carolina which is planning to submit a grant to follow a cohort of children from birth through age 8 years to investigate hormone levels in cord blood and subsequent childhood weight, height, diet and physical activity.

Key Research Accomplishments

- Completed Task 1.a. by auditing Pathology of Neoplasia.
- Gained knowledge of analysis of dietary intake by co-authoring the manuscript "Dietary exposures and oral precancerous lesions in Srikakulam District, Andhra Pradesh, India".
- Gained knowledge of analysis of anthropometric measurements by presenting the poster "Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population".
- Partially completed Task 1.e. by submitting an Idea Award to the Department of Defense entitled "Prenatal and Postnatal Growth, Hormones, Diet and Breast Cancer".
- Analyzed data from the Shanghai Breast Cancer Study and authored the article "Abortion history and breast cancer risk: Results from the Shanghai Breast Cancer Study".
- Began work on Task 2.f. by participating in a childhood obesity work group at the University of South Carolina.

Reportable Outcomes

1) Manuscripts

Sanderson M, Shu X-O, Jin F, Dai Q, Wen W-Q, Hui Y, Gao Y-T, Zheng W. Abortion history and breast cancer risk: Results from the Shanghai Breast Cancer Study. Int J Cancer 2001;92:899-905.

Hebert JR, Gupta PC, Bhonsle RB, Mehta H, Zheng W, Sanderson M, Teas J. Dietary exposures and oral precancerous lesions in Srikakulam District, Andhra Pradesh, India. Public Health Nutr (Submitted January 2001).

2) Abstracts

Sanderson M, Shu XO, Jin F, Dai Q, Ruan Z, Gao YT, Zheng W. Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population. Am J Epidemiol 2001;153:75.

3) Grants

Grant Name:	Prenatal and Postnatal Growth, Hormones, Diet and Breast Cancer
Funding Agency:	U.S. Army Medical Research and Materiel Command
Period of Funding:	April 1, 2001 – March 31, 2006 ($898,009)
Role:	Principal Investigator (20% effort years 1-5, 0% support years 1-3)

Conclusions

To date, my breast cancer research has focused on surrogate markers of intrauterine exposure to estrogen and subsequent breast cancer. This research has led me to the understanding that prenatal and postnatal growth represent critical periods in breast carcinogenesis, in large part due to exposure to estrogen and other hormones/growth factors. Clearly, dietary intake is associated with prenatal and postnatal growth. Diet also has been related to estrogen, IGF1 and other hormones/growth factors, and to breast cancer. Elevated levels of IGF1 and insulin, and abdominal obesity are markers for insulin resistance, which has been positively associated with breast cancer in several studies.

This Career Development Award will investigate an area of recent interest in breast cancer, the interrelationships of prenatal and postnatal growth, hormones, diet, and breast cancer. The possibility that insulin resistance may tie these factors together has led to my goal of studying the association between insulin resistance and breast cancer. A secondary goal is to assess the influence of genetic susceptibility, diet and physical activity on this association.

South Carolina is an exceptional location to perform breast cancer research because one-third of the population are African-American. African-American women have a high incidence of breast cancer, and a higher breast cancer mortality rate than white women. This research will allow us to investigate whether the elevated risk of breast cancer among African-American women in South Carolina may be related to their higher genetic susceptibility to insulin resistance. Women tend to develop insulin resistance if they are genetically susceptible, gain excess weight due to physical inactivity, and consume a high-fat, low-fiber diet during adolescence and adulthood. It is clear that this area of research has promise with regard to explaining the different breast cancer incidence and mortality rates by ethnicity.

In summary, the interrelationships of prenatal and postnatal growth, hormones, diet and breast cancer are complex. There is compelling evidence that insulin resistance may tie these relationships together, and may help explain the elevated risk of breast cancer among certain ethnic groups in the US. Should insulin resistance prove to be associated with breast cancer, the possibility that genetic susceptibility and adolescent/adult diet and physical activity may modify this association will be useful in targeting interventions for women at high risk for breast cancer.

References

Sanderson M, Shu X-O, Jin F, Dai Q, Wen W-Q, Hui Y, Gao Y-T, Zheng W. Abortion history and breast cancer risk: Results from the Shanghai Breast Cancer Study. Int J Cancer 2001;92:899-905.

Hebert JR, Gupta PC, Bhonsle RB, Mehta H, Zheng W, Sanderson M, Teas J. Dietary exposures and oral precancerous lesions in Srikakulam District, Andhra Pradesh, India. Public Health Nutr (Submitted January 2001).

Sanderson M, Shu XO, Jin F, Dai Q, Ruan Z, Gao YT, Zheng W. Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population. Am J Epidemiol 2001;153:75.

Appendices

Appendix A

Neoplasia
Pathology 710
Tuesdays and Thursdays from 3:30 – 5:00
Department of Microbiology and Immunology Conference Room
Building 2, Room C4
(28 Class Periods)

Faculty: Kim E. Creek, Ph.D., will serve as course coordinator.
Office, Building 4, Room C7
Phone: 733-3153
Email: creek@med.sc.edu

Neoplasia will be a "team" taught course bringing together the considerable expertise in cancer biology that exists within the USC community. Each instructor will present information in their area of expertise. The format of presentation, as well as the material to be presented, is entirely up to each faculty member participating in the course.

Background: This is a required course of all graduate students who wish to specialize in the Molecular Oncology Focus Area and will usually be taken by students entering their second year of study. Since all students in this course have a strong interest in oncology, the course will be taught at a level to provide students with the most up-to-date information possible and at a level appropriate for students in their second year of graduate study. The topics to be presented cover most areas of neoplasia and the basic science of oncology. We realize that it is impossible in a one semester course to cover all aspects of this extremely large and broad topic. However, we will emphasize the topics and areas that I believe are most appropriate for graduate students in a Biomedical Sciences Program.

Textbook: The required textbook for the course is "*The Basic Science of Oncology*" 3rd Edition, by I.F. Tannock and R.P. Hill, 1998. The book is available for purchase in the School of Medicine bookstore. Additional reference books are: "*The Biological Basis of Cancer*" by R.G. McKinnell, R.E. Parchment, A.O. Perantoni, and G.B. Pierce, 1998 and "*Introduction to the Cellular and Molecular Biology of Cancer*" 3rd Edition, by L.M. Franks and N.M. Teich, 1997.

The following web site http://www.carcin.oupjournals.org/content/vol21/issue3/ has the full text of a recent issue of the journal *Carcinogenesis* that contains several review articles on various aspects of cancer biology. This should serve as a valuable source of very current information.

Grading: The final grade will be based on two "take-home" exams (50% each exam), consisting of questions supplied by the various instructors. The exact dates of the exams will be announced in class.

Schedule of Lectures

August 24	Introduction to Course (Creek)
August 29	Overview of Neoplasia (Lill)
August 31	Overview of Neoplasia (Lill)
September 5	Tumor Nomenclature (Lill)
September 7	Mechanisms of Metastasis (Lill)
September 12	Viral Carcinogenesis (Pirisi)
September 14	Viral Carcinogenesis (Pirisi)
September 19	Chemical Carcinogenesis (Farber)
September 21	Chemical Carcinogenesis (Farber)
September 26	Multistep Nature of Cancer (Farber)
September 28	Cell Cycle (Pirisi)
October 3	Oncogenes/Apoptosis/Telomerase (Patton)
October 5	Tumor Suppressor Genes (Patton)
October 10	Growth Factors/Signaling Pathways in Cancer (Creek)
October 12	Growth Factors/Signaling Pathways in Cancer (Creek)

October 17 No Class (Fall Break)

October 19 Epidemiology of Cancer (Maureen Sanderson)

October 24 Hormones and Cancer (Housley)

October 26 Hormones and Cancer (Housley)

October 31 Breast Cancer (Cunningham)

November 2 Prostate Cancer (Bostick)

November 7 No Class (Election Day)

November 9 Colon Cancer (Wargovich)

November 14 Chemoprevention (Wargovich)

November 16 Diet and Cancer (Wargovich)

November 21 Immunology of Cancer (Lamb)

November 23 No Class (Thanksgiving)

November 28 Molecular Epidemiology (Dawen)

November 30 Principles of Chemotherapy (Spencer)

December 5 Immunotherapy (Spencer)

December 7 Gene Therapy (Spencer)

Appendix B

DIETARY EXPOSURES AND ORAL PRECANCEROUS LESIONS IN SRIKAKULAM DISTRICT, ANDHRA PRADESH, INDIA

James R. Hebert, Sc.D.[1,2,3,4]

Prakash C. Gupta, Sc.D.[5]

Ramesh B. Bhonsle, B.D.S.[5]

Hemali Mehta, M. Sc.[5]

Wei Zheng, M.D., Ph.D.[1,3]

Maureen Sanderson, R.D., Ph.D.[1,2,3]

Jane Teas, Ph.D.[2,3,6]

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2. Nutrition Center, University of South Carolina School of Public Health, Columbia, SC 29208, USA.
3. Division of Population Studies, South Carolina Cancer Center, 15 Medical Park, Columbia, SC 29203, USA
4. Author to whom correspondence should be addressed.
5. Epidemiology Research Unit, Tata Institute of Fundamental Research, Homi Bhabha Road, Bombay 400005, India.
6. Department of Environmental Health Sciences, University of South Carolina School of Public Health, Columbia, SC 29208, USA

Keywords: India, oral neoplasms, precancerous conditions, dietary nutrients.

ABSTRACT

Objective: To test the effect of dietary nutrients on oral precancerous lesions in a reverse-smoking (i.e., smoking with the glowing end inside the mouth) population in South India.

Design: Case-control. Cases with precancerous lesions were matched to an equal number of lesion-free controls matched on: age (±5 years), sex, and village. All subjects used tobacco in some form. Dietary data were obtained using an interviewer-administered food frequency questionnaire, designed for use in this population. All interviews were conducted blinded to the disease status of the subject. Data were analyzed using logistic regression.

Setting: 19 rural villages in Srikakulam district, Andhra Pradesh.

Subjects: From a survey of 6007 tobacco users 485 (79% women) were found to have precancerous, mostly palatal, lesions (cases), and 487 lesion-free subjects were selected as controls.

Results: All eligible subjects consented to participate and nearly all (>99%) had complete data for analyses. Reverse smoking was the most common form of tobacco use among cases (81.9%) and controls (73.5%), and reverse smokers were 5.19 times more likely than chewers to have these lesions (95% confidence interval = 1.35, 19.9). After controlling for relevant covariates, including the type of tobacco use, protective linear effects were observed for zinc (70% reduction across the interquartile range, $p < 0.002$), calcium (34% reduction, $p < 0.002$), fibre (30% reduction, $p < 0.009$), riboflavin (22% reduction, $p < 0.03$), and iron (17% reduction, $p < 0.05$).

Conclusions: Several dietary nutrients appear to protect against oral precancerous lesions that are strongly associated with reverse smoking. The results of this study indicate scope for targeting dietary factors in preventing oral cancer, which should be coupled with aggressive anti-tobacco use efforts.

Running Head: Diet and Oral Precancerous Lesions in India

Appendix C

SUPPLEMENT TO:
American Journal of
EPIDEMIOLOGY
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Abstracts

2001 Congress of Epidemiology

A Joint Meeting of the

American College of Epidemiology
American Public Health Association
(Epidemiology Section)
Canadian Society for Epidemiology
and Biostatistics
Society for Epidemiologic Research

Toronto, Canada, June 13-16, 2001

CONGRESS OF EPIDEMIOLOGY 2001

Founded in 1920 by W. H. Welch and W. H. Howell as the American Journal of Hygiene
at the Johns Hopkins School of Hygiene and Public Health

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REPRODUCTIVE FACTORS AND PREMENOPAUSAL BREAST CANCER SURVIVAL.

SM Enger* and L Bernstein (University of Southern California, Los Angeles, CA 90033)

The relationship of reproductive factors with premenopausal breast cancer risk has been studied extensively, but less is known about the role of these factors on survival. We studied the role of several reproductive factors on a woman's risk of dying from breast cancer, among breast cancer patients who participated in a population-based case-control study of premenopausal breast cancer in Los Angeles County. Participants were 744 women aged 40 years or younger, diagnosed with breast cancer from 07/83 through 12/88. We followed-up the women for vital status through 05/98 (median follow-up 8.8 years) and observed 231 deaths. We computed hazard rates (HR) and 95% confidence intervals (CI) using Cox proportional hazards regression. Women with at least 1 full-term pregnancy had a reduced risk of dying from their breast cancer compared to women with no full-term pregnancies (HR 0.77, 95% CI 0.59-1.01). Among parous women, those with a recent full-term pregnancy (within 5 years of their breast cancer diagnosis) had a reduced risk of dying from their breast cancer compared to women whose last full-term pregnancy was more than 5 years before diagnosis (HR 0.65, 95% CI 0.42-0.99). The results were consistent within categories of stage at diagnosis. Age at first full-term pregnancy and breast-feeding history were not clearly associated with risk of dying. Our findings suggest that parous women and women with recent pregnancies who develop breast cancer may be more likely to develop tumors with better prognosis than nulliparous women and women without recent pregnancies.

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OCCUPATIONS AND THE RISK OF BREAST CANCER AMONG CHINESE WOMEN .

KM Gardner*, XO Shu, F Jin, Q Dai, Z Ruan, SJ Thompson, JR Hussey, YT Gao and W Zheng (Vanderbilt University, Nashville, TN 37232)

Although an elevated risk of breast cancer has been suggested for a number of occupations, many earlier studies were limited by selection biases, incomplete assessment of job histories and the inability to control for confounding. We examined the relationship between lifetime occupational history and breast cancer risk using data from a population-based case-control study of 1458 cases and 1556 age-matched controls (90% response rate) conducted in Shanghai, China. Unconditional logistic regression models were used to derive odds ratios (ORs) and 95% confidence intervals (95% CIs) of breast cancer associated with occupations and duration of employment adjusting for non-occupational risk factors. We found the following occupations were associated with an increased risk of breast cancer: laboratory technicians (OR 9.94, 95% CI 1.20-82.37), telephone and telegraph operators (OR 4.63, 95% CI, 1.85-11.59), leather and fur processors (OR 3.25, 95% CI 1.11-9.53), glass-related workers (OR 2.08, 95% CI 1.14-3.82) and farmers working >10 years (OR 2.08, 95% CI 1.15-3.74). A dose-response pattern for years of specific employment was observed for leather and fur processors (p=0.02) and glass-related workers (p=0.01). Stratified analysis also revealed a dose response relationship between years of employment and the risk of premenopausal breast cancer among inspector and product analysts (p=0.02) and postmenopausal breast cancer among farmers (p=0.04). This study suggests that occupations that likely involve exposure to xenoestrogens, chemicals structurally similar to estrogen, may increase the risk of breast cancer.

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WEIGHT AT BIRTH AND ADOLESCENCE AND PREMENOPAUSAL BREAST CANCER RISK IN A LOW-RISK POPULATION.

M Sanderson*, XO Shu, F Jin, Q Dai, Z Ruan, YT Gao and W Zheng (University of South Carolina, Columbia, SC 29208)

Premenopausal breast cancer has been linked to high birth weight, and conversely to low adolescent and adult weight. The authors used data from a population-based case-control study of breast cancer among women age 25 to 64 conducted between 1996 and 1998 in urban Shanghai to assess weight at birth and adolescence and breast cancer risk. In-person interviews were completed with 1459 incident breast cancer cases ascertained through a population-based cancer registry, and 1556 controls randomly selected from the general population in Shanghai (with respective response rates of 91% and 90%). This analysis is restricted to premenopausal women (903 cases and 949 controls); maternal report of birth weight and adolescent weight was available for 296 cases and 395 controls. After adjustment for confounding, women who were 4000 grams or more at birth were not at increased risk of breast cancer (odds ratio (OR)=0.6; 95% confidence interval (CI) 0.3-1.3) relative to women whose birth weight was 2500 to 2999 grams. No association was apparent for breast cancer associated with heavier than average weight at age 15 based on self-report (OR=1.1; 95% CI 0.8-1.4); however, there appeared to be a reduced risk of breast cancer based on maternal report (OR=0.6; 95% CI 0.3-1.0). Neither adolescent nor adult weight modified the effect of birth weight on breast cancer risk. These results suggest that the effect of weight early in life on premenopausal breast cancer risk may differ in this low-risk population.

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SMALL AREA VARIATION IN BREAST CANCER SURVIVAL.

DI Gregorio*, M Kulldorff and G Phillips (University of Connecticut School of Medicine, Farmington, CT 06030-6325)

By 1997, 27% of the 31,011 Connecticut women diagnosed with breast cancer between 1984 and 1995 had died of their disease. It is not known whether geographic differences in survival exist, nor the extent to which differences are confined to specific localities. To consider these questions we evaluated geographic variation regarding the vital status of in situ or invasive breast cancer cases (ICD-9-CM 174) during this 14 year period. Latitude- longitude coordinates for a woman's place of residence at diagnosis were examined using a spatial scan statistic to detect geographic excess in death rates among cases and test the statistical significance of results without prior assumptions about the size or location of such areas. Relative to the Statewide experience, the risk of death with breast cancer was significantly higher (<0.01) in Waterbury (RR=1.43), Bridgeport (1.46), Hartford-E. Hartford (1.31) and New Haven (1.25). These 'hot spots' correspond to geographic variation in population and disease attributes. Survival rates did not vary geographically among non-white women, but among whites, survival was significantly poorer for those living in Waterbury (RR=1.44), Hartford-E. Hartford (1.38) and Bridgeport (1.33). Geographic differences in survival with early disease were not found, but among those with late-stage disease at diagnosis, women from New Haven had significantly poorer survival than others around the state (RR=1.27). Evidence of geographic variation in breast cancer survival may highlight aspects of disease etiology, care seeking and/or clinical service delivery that can inform us about the causes and control of this disease.

Appendix D

Technical Abstract
Prenatal and Postnatal Growth, Hormones, Diet and Breast Cancer
Maureen Sanderson

Background: Endogenous estrogen has been implicated as a causal factor for breast cancer and critical periods of exposure are thought to be *in utero*, following menarche and during perimenopause. Factors associated with intrauterine estrogen exposure and prenatal growth, including preeclampsia and infant birth weight, have been related to breast cancer. Breast cancer associated with measures of postnatal growth, such as adolescent and adult weight and height, appears to differ by menopausal status which, in part, may be explained by hormonal changes. Lower adult estrogen levels have been associated with low-fat, high-fiber diets. Insulin-like growth factor 1 (IGF1), which has been linked to breast cancer in several studies, may act in combination with estrogen. IGF1 concentrations are positively associated with height and body mass, and adults who were born at relatively low weights and who then become obese may have increased IGF1 and insulin levels. Decreased IGF1 concentrations have been associated with a low-calorie diet, and retinoids and vitamin D analogues may also lower IGF1 levels. Insulin resistance, characterized by high levels of IGF1 and insulin, and abdominal obesity, has been linked to breast cancer. The elevated risk of breast cancer among some ethnic groups within the United States (US) may be related to their higher genetic susceptibility to insulin resistance brought on by excess weight gain, and a high-fat, low-fiber diet.

Objective/Hypothesis: The purpose of this proposed Idea Award is to expand a newly funded Department of Defense (DOD) quasi-prospective study of breast cancer to collect, process and analyze blood for estradiol (E2), sex hormone-binding globulin (SHBG), IGF1, insulin-like growth factor binding protein 3 (IGFBP3), insulin and glucose. The primary hypotheses are: 1) insulin resistance, defined as high levels of insulin and glucose or type 2 diabetes, will be positively associated with breast cancer, and 2) the insulin resistance-breast cancer association will be mediated, in part, through abdominal obesity, E2, SHBG, IGF1, and IGFBP3, alone or in combination. A secondary hypothesis is that the insulin resistance-breast cancer relation will be modified by birthweight, age at which adult height was achieved, diet, physical activity, and weight gain, alone or in combination.

Specific Aims: The specific aims of this proposed case-control study are: 1) to obtain information on type 2 diabetes, waist circumference, body mass index (BMI), birthweight, age at which adult height was achieved, diet, physical activity, and weight gain, and to collect pre-diagnostic blood, 2) to assay blood for E2, SHBG, IGF1, IGFBP3, insulin and glucose, and 3) to perform statistical analyses to assess the association between insulin resistance and breast cancer risk, while accounting for confounding and effect modification. The principal investigator received a Career Development Award (CDA) from DOD last year to study the interrelationships of prenatal and postnatal growth, hormones, diet and breast cancer. This proposed study would accomplish one aim of that CDA of obtaining funding to conduct case-control studies of the insulin resistance-breast cancer relationship.

Study Design: The quasi-prospective or Parent Study will consist of 648 incident breast cancer cases and 2592 controls who undergo diagnostic mammogram for breast cancer and are found later to be cancer free. The Parent Study is quasi-prospective in that women will be interviewed and biological samples will be collected prior to diagnosis. This proposed study will recruit an additional 652 cases, and will select 1300 healthy women who receive a negative screening mammogram to form the control group. After completing a risk factor questionnaire, women

will be asked to provide a fasting blood sample during their follow-up visit. The blood will be assayed for E2, SHBG, IGF1, IGFBP3, insulin and glucose.

Relevance: The interrelationships of prenatal and postnatal growth, hormones, diet and breast cancer are complex. There is compelling evidence that insulin resistance may tie these relationships together, and may help explain the elevated risk of breast cancer among certain ethnic groups in the US. Should insulin resistance prove to be associated with breast cancer, the possibility that genetic susceptibility and adolescent/adult diet and physical activity may modify this association will be useful in targeting interventions for women at high risk for breast cancer.

Statement of Work

Prenatal and Postnatal Growth, Hormones, Diet and Breast Cancer

Task 1. Preliminary Activities, Months 1-3:

a. Refine data collection protocol and instruments
b. Train study staff
c. Develop tracking system and data entry programs
d. Write manual of operations
e. Pretest instruments and computer programs

Task 2. Data and Specimen Collection, Months 4-54:

a. Identify and recruit 1300 cases (648 through the Parent study and 652 through this proposed study) and 1300 controls
b. Complete questionnaires to obtain information on type 2 diabetes, birthweight, age at which adult height was achieved, diet, physical activity, weight gain, lifestyle factors, demographic variables, family and personal health-related history, social desirability and social approval
c. Take anthropometric measurements
d. Collect pre-diagnostic blood
e. Abstract medical records for relevant health history and pathology data

Task 3. Laboratory Assays, Months 4-57:

a. Refine protocols for laboratory work
b. Process and store blood samples
c. Complete enzyme-linked immunosorbent assays (ELISA) for IGF1 and IGFBP3, enzyme immunoassays (EIA) for E2 and insulin, radioimmunoassays (RIA) for SHBG, and measure glucose using the glucose oxidase method

Task 4. Data Management and Analysis, Months 4-60:

a. Complete data entry of all questionnaires and assays
b. Perform interim statistical analyses in months 13, 25 and 37 to assess data quality
c. Perform final statistical analysis to test study hypotheses
d. Prepare manuscripts to report study results
e. Archive datasets for future analyses and future patient follow-up

Appendix E

Int. J. Cancer: **92**, 899–905 (2001)

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ABORTION HISTORY AND BREAST CANCER RISK: RESULTS FROM THE SHANGHAI BREAST CANCER STUDY

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Studies of the association between induced abortion and breast cancer risk have been inconsistent, perhaps due to underreporting of abortions. Induced abortion is a well-accepted family planning procedure in China, and women who have several induced abortions do not feel stigmatized. The authors used data from a population-based case-control study of breast cancer among women age 25–64 conducted between 1996 and 1998 in urban Shanghai to assess whether a history of and the number of induced abortions were related to breast cancer risk. In-person interviews were completed with 1,459 incident breast cancer cases ascertained through a population-based cancer registry, and 1,556 controls randomly selected from the general population in Shanghai (with respective response rates of 91% and 90%). After adjusting for confounding, there was no relation between ever having had an induced abortion and breast cancer (odds ratio [OR] = 0.9, 95% confidence interval [CI] 0.7–1.2). Women who had 3 or more induced abortions were not at increased risk of premenopausal breast cancer (OR = 0.9, 95% CI 0.6–1.4) or postmenopausal breast cancer (OR = 1.3, 95% CI 0.8–2.3). These results suggest that a history of several induced abortions has little influence on breast cancer risk in Chinese women.

Key words: *abortion; breast cancer; pregnancy; case-control studies*

Studies of induced abortion and breast cancer risk have been inconsistent. Underreporting of induced abortion is suspected,[1] which may be reflected in the low reported percentages of women who had undergone the procedure in these studies. In the majority of previous studies of this association fewer than 20% of women have reported induced abortions. The Iowa Women's Health Study, a cohort study, had the lowest percentage of reported induced abortions (2%), and found no association between induced abortion and breast cancer risk (OR = 1.1, 95% CI 0.8–1.6).[2] An intermediate percentage of reported induced abortions (39%) was found in a Greek case-control study that reported an elevated risk of breast cancer associated with induced abortion (OR = 1.51, 95% CI 1.28–1.84).[3] The highest percentage of reported induced abortions (76%) was seen in a Russian case-control study that reported no association for 1 abortion (OR = 1.0, 95% CI 0.7–1.4) and a borderline reduced risk for 2 or more abortions (OR = 0.7, 95% CI 0.6–1.0).[4] Remennick[5] postulated that should induced abortion be related to breast cancer Russian women may be at a greater risk given the extremely frequent use of the procedure. The same may be true of women in China that had 1 of the highest induced abortion rates in the world during the childbearing years for the majority of women in this study.[6]

This study was conducted to assess whether a history of and the number of induced abortions were related to breast cancer risk. The lack of social stigma associated with induced abortion in China may limit the amount of underreporting of the procedure and present a clearer picture of this association.

MATERIAL AND METHODS

Detailed methods of this population-based case-control study appear elsewhere.[7] Briefly, all women age 25–64 years who were permanent residents of urban Shanghai at the time of diagnosis of first primary invasive breast cancer (August 1996 through March 1998) were eligible for the study. Two senior pathologists histologically confirmed all diagnoses. We used rapid case ascertainment supplemented by the Shanghai Cancer Registry to identify breast cancer cases who had no prior history of cancer and were alive at the time of interview. A total of 1,459 breast cancer cases (91.1% of eligible cases) completed a standardized in-person interview. Of eligible cases, 109 refused (6.8%), 17 died before the interview (1.1%), and 17 were not located (1.1%).

The Shanghai Resident Registry, a listing of all permanent residents of urban Shanghai, was used to randomly select controls. Controls were frequency matched to cases on age (5-year interval) based on the number of incident breast cancer cases by age group reported to the Shanghai Cancer Registry from 1990–1993. Women who did not reside at the registered address at the time of the study were ineligible. A total of 1,556 controls (90.4% of eligible controls) completed a standardized in-person interview. The remaining 166 eligible controls (9.6%) refused participation. Two women died before the interview and were excluded. Over 95% of women had a live birth, therefore we restricted this analysis to parous women (1,385 cases, 1,495 controls).

The study was approved by a local institutional review board. Women were interviewed at hospitals (cases) or at home (cases and controls) by trained interviewers. The questionnaire collected information on demographic factors, reproductive and medical histories, family history of cancer, use of oral contraceptives or hormone replacement therapy, diet, physical activity, lifestyle factors, and body size. Women provided detailed information on each pregnancy, including its outcome and gestational length. After completing the interview, women were weighed and had their standing and sitting height, and waist and hip circumferences measured. Women were classified as premenopausal if they reported having menstrual periods within the past 12 months. Postmenopausal women were those who had undergone natural or surgical menopause. Information on exposures pertained to the period before an assigned reference date, the diagnosis date for breast cancer cases and a similar date for controls.

We used unconditional logistic regression to estimate the relative risk of breast cancer associated with abortion history while controlling for confounders.[8] All variables other than age (continuous) were entered into models as dummy variables. Variables were considered confounders of the relationship be-

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TABLE 1 – COMPARISON OF CASES AND CONTROLS ON BREAST CANCER RISK FACTORS

	Cases (n = 1,385)		Controls (n = 1,495)		OR	(95% CI)	Age-adjusted	
	No.	%	No.	%			OR	(95% CI)
Age (years)								
25–34	37	2.7	69	4.6	1.0	(reference)		
35–44	494	35.7	551	36.9	1.7	(1.1–2.5)		
45–54	538	38.8	497	33.2	2.0	(1.3–3.1)		
55–64	316	22.8	378	25.3	1.6	(1.0–2.4)		
Education								
Never	51	3.7	84	5.6	1.0	(reference)	1.0	(reference)
Elementary	118	8.5	127	8.5	1.5	(1.0–2.4)	1.6	(1.0–2.5)
Middle + High	1,036	74.8	1,130	75.6	1.5	(1.0–2.2)	1.9	(1.3–2.8)
Prof. + College	180	13.0	154	10.3	1.9	(1.3–2.9)	2.2	(1.5–3.4)
Per capita income (last year, yuan)								
<4,000	261	18.9	276	18.5	1.0	(reference)	1.0	(reference)
4,000–5,999	450	32.5	485	32.5	1.0	(0.8–1.2)	1.0	(0.8–1.3)
6,000–7,999	180	13.0	208	13.9	0.9	(0.7–1.2)	0.9	(0.7–1.2)
8,000–8,999	280	20.2	346	23.1	0.9	(0.7–1.1)	0.9	(0.7–1.1)
≥9,000	213	15.4	180	12.0	1.3	(1.0–1.5)	1.3	(1.0–1.7)
Breast cancer among first-degree relatives								
No	1,333	96.3	1,459	97.6	1.0	(reference)	1.0	(reference)
Yes	52	3.7	36	2.4	1.6	(1.0–2.4)	1.6	(1.0–2.4)
Ever had breast fibroadenoma								
No	1,253	90.5	1,422	95.1	1.0	(reference)	1.0	(reference)
Yes	131	9.5	73	4.9	2.0	(1.5–2.7)	2.1	(1.5–2.8)
Age at menarche (years)								
10–12	128	9.3	123	8.2	1.0	(reference)	1.0	(reference)
13–16	1,115	80.5	1,150	77.0	0.9	(0.7–1.2)	0.9	(0.7–1.2)
≥17	141	10.2	221	14.8	0.6	(0.4–0.9)	0.6	(0.4–0.8)
Menopause								
No	903	65.4	949	63.6	1.0	(reference)	1.0	(reference)
Yes	478	34.6	543	36.4	0.9	(0.8–1.1)	0.6	(0.5–0.8)
Age at menopause								
<45	77	16.1	116	21.6	1.0	(reference)	1.0	(reference)
45–49	203	42.6	219	40.7	1.4	(1.0–2.0)	1.5	(1.0–2.1)
≥50	197	41.3	203	37.7	1.5	(1.0–2.1)	1.6	(1.1–2.3)
Body mass index (by quartile)								
≤20.70	281	20.3	373	25.0	1.0	(reference)	1.0	(reference)
20.71–22.79	331	24.0	373	25.0	1.2	(1.0–1.5)	1.2	(0.9–1.5)
22.80–25.10	373	27.0	376	25.1	1.3	(1.1–1.6)	1.3	(1.0–1.6)
>25.10	397	28.7	372	24.9	1.4	(1.2–1.8)	1.4	(1.1–1.7)
Waist-to-hip ratio (by quartile)								
≤0.764	265	19.2	373	25.0	1.0	(reference)	1.0	(reference)
≤0.765–0.800	351	25.4	398	26.6	1.2	(1.0–1.5)	1.2	(1.0–1.5)
0.801–0.835	348	25.2	345	23.1	1.4	(1.1–1.8)	1.4	(1.1–1.7)
>0.835	418	30.2	378	25.3	1.6	(1.3–1.9)	1.5	(1.2–1.9)
Alcohol consumption								
Never	1,329	96.1	1,432	96.0	1.0	(reference)	1.0	(reference)
Ever	54	3.9	60	4.0	1.0	(0.7–1.4)	1.0	(0.7–1.4)
Oral contraceptive use								
Never	1,068	77.1	1,172	78.4	1.0	(reference)	1.0	(reference)
Ever	317	22.9	323	21.6	1.1	(0.9–1.3)	1.0	(0.9–1.2)
Physical activity during past 10 years								
Never	1,128	81.5	1,117	74.8	1.0	(reference)	1.0	(reference)
Ever	256	18.5	377	25.2	0.7	(0.6–0.8)	0.6	(0.5–0.7)
Age at first live birth								
<20	62	4.5	73	4.9	1.0	(reference)	1.0	(reference)
20–24	303	21.9	360	24.1	1.0	(0.7–1.4)	1.1	(0.8–1.6)
25–29	712	51.4	816	54.6	1.0	(0.7–1.5)	1.3	(0.9–1.8)
30–34	248	17.9	206	13.7	1.4	(1.0–2.1)	1.7	(1.1–2.6)
35+	60	4.3	40	2.7	1.8	(1.1–3.0)	2.1	(1.2–3.6)
Number of live births								
1	912	65.9	975	65.2	1.0	(reference)	1.0	(reference)
2	317	22.9	333	22.3	1.0	(0.9–1.2)	0.8	(0.6–1.0)
3	104	7.5	121	8.1	0.9	(0.7–1.2)	0.6	(0.4–0.9)
≥4	52	3.7	66	4.4	0.8	(0.6–1.2)	0.5	(0.4–0.8)
Cumulative duration of breastfeeding								
No	302	21.8	300	20.1	1.0	(reference)	1.0	(reference)
1–11 months	593	42.8	638	42.7	0.9	(0.8–1.1)	0.9	(0.8–1.1)
12–23 months	275	19.9	307	20.5	0.9	(0.7–1.1)	0.8	(0.6–1.0)
≥24 months	215	15.5	250	16.7	0.9	(0.7–1.1)	0.7	(0.5–0.9)
Stillbirth								
Never	1,357	98.0	1,472	98.5	1.0	(reference)	1.0	(reference)
Ever	28	2.0	23	1.5	1.3	(0.8–2.3)	1.3	(0.8–2.3)

TABLE II – ODDS RATIOS OF BREAST CANCER ASSOCIATED WITH INDUCED ABORTION

	Premenopausal women			Postmenopausal women		
	Case/ctrl	OR[1]	(95% CI)	Case/ctrl	OR[1]	(95% CI)
Abortion						
Never	283/292	1.0	(reference)	188/209	1.0	(reference)
Ever	620/657	1.0	(0.8–1.2)	290/334	0.9	(0.7–1.2)
Number of abortions						
1	404/394	1.1	(0.9–1.3)	152/206	0.8	(0.6–1.1)
2	170/215	0.8	(0.6–1.0)	100/97	1.0	(0.7–1.5)
≥3	46/48	0.9	(0.6–1.4)	38/31	1.3	(0.8–2.3)
		$p = 0.13$			$p = 0.50$	
Age at first abortion (years)						
<25	40/69	0.7	(0.4–1.0)	41/35	1.1	(0.7–1.9)
25–29	296/328	1.0	(0.8–1.2)	113/144	0.8	(0.6–1.2)
30–34	205/179	1.1	(0.9–1.5)	95/115	0.9	(0.6–1.3)
≥35	77/81	0.9	(0.6–1.3)	41/39	1.1	(0.7–1.8)
		$p = 0.39$			$p = 0.57$	
Time of first abortion						
Before first live birth	72/86	1.0	(0.7–1.4)	11/13	0.9	(0.4–2.1)
After first live birth	548/571	1.0	(0.8–1.2)	279/321	0.9	(0.7–1.2)
Number of abortions relative to first live birth						
Before first live birth						
1	64/76	1.0	(0.7–1.5)	9/13	0.7	(0.3–1.8)
≥2	8/10	1.0	(0.4–2.7)	2/0	—	
		$p = 0.81$			$p = 0.70$	
After first live birth						
1	368/360	1.1	(0.8–1.3)	147/202	0.8	(0.6–1.1)
2	139/173	0.8	(0.6–1.0)	96/91	1.0	(0.7–1.5)
≥3	41/38	0.9	(0.6–1.5)	36/28	1.4	(0.8–2.5)
		$p = 0.12$			$p = 0.09$	
Interval between first abortion and reference date (years)						
0–9	126/167	1.0	(0.7–1.4)	5/4	1.9	(0.5–8.0)
10–14	209/251	0.9	(0.7–1.2)	15/19	0.9	(0.4–1.9)
15–19	171/143	1.1	(0.8–1.5)	31/32	1.1	(0.6–1.9)
≥20	112/96	0.8	(0.6–1.2)	239/278	0.9	(0.7–1.2)
		$p = 0.32$			$p = 0.78$	
Gestational length of first abortion (weeks)						
1–8	503/545	0.9	(0.8–1.2)	230/262	0.9	(0.7–1.2)
9–12	89/79	1.2	(0.8–1.7)	45/57	0.9	(0.6–1.4)
≥13	25/32	0.9	(0.5–1.6)	14/14	1.3	(0.6–2.9)
		$p = 0.50$			$p = 0.43$	

[1]Adjusted for age, education, family history of breast cancer in first-degree relative, history of fibroadenoma, age at menarche, age at menopause, waist-to-hip ratio, physical activity, duration of breastfeeding, spontaneous abortion, age at first live birth, and number of live births.

tween abortion history and breast cancer risk if their addition to the model changed the unadjusted odds ratio by 10% or more. Product terms between induced abortion and potential effect modifiers were added to the model to assess departure from a multiplicative relation. In multiple logistic regression models, we assessed linear trend by treating categorical variables as continuous variables.

RESULTS

Table I presents odds ratios (OR) and 95% confidence intervals (CI) for known breast cancer risk factors comparing cases and controls unadjusted and adjusted for age. Breast cancer cases were more likely than controls to be older, more highly educated, have a first-degree relative with breast cancer, have a history of fibroadenoma, have an earlier age at menarche, be premenopausal, have a later age at menopause, have a higher body mass index, have a higher waist-to-hip ratio, have a later age at first birth, and have fewer live births. Cases were less likely than controls to engage in physical activity and to have breast fed for 12 months or more. With the exception of age, none of the preceding variables were confounders of the association between induced abortion and breast cancer. Adjustment was made for these variables, however, to be consistent with the majority of studies on this topic. In addition, the induced abortion analyses are adjusted for a history of spontaneous abortion, and the spontaneous abortion analyses are adjusted for a history of induced abortion. Although there was no evidence of effect modification, analyses are presented separately by menopausal status because the effect of some hormonal exposures on breast cancer risk is thought to differ by menopausal status.

Table II shows results for the induced abortion and breast cancer association stratified by menopausal status. The percentage of women who had an induced abortion was slightly higher among premenopausal women (69% of cases and controls) than among postmenopausal women (61% of cases and 62% of controls). After adjusting for confounding, there was no overall relation between ever having had an induced abortion and breast cancer (OR = 1.0, 95% CI 0.8–1.2). Women who had 3 or more induced abortions were not at increased risk of premenopausal breast cancer (OR = 0.9, 95% CI 0.6–1.4) or postmenopausal breast cancer (OR = 1.3, 95% CI 0.8–2.3). Among premenopausal and postmenopausal women, there was little effect on breast cancer risk of age at first induced abortion, timing of first induced abortion relative to timing of first live birth, number of induced abortions relative to timing of first live birth, interval between first induced abortion and reference date, or gestational length of first induced abortion.

In analyzing the number of induced abortions and the age at first induced abortion by menopausal status, we stratified by age at first live birth and number of live births (Table III). Among premenopausal women, the effect of having 3 or more induced abortions differed by age at first live birth (≤25 years: OR = 0.5, 95% CI 0.2–1.1; >25 years: OR = 1.4, 95% CI 0.8–2.5). Postmenopausal women who had 3 or more induced abortions and 2 or more live

TABLE III – ODDS RATIOS OF BREAST CANCER ASSOCIATED WITH INDUCED ABORTION BY CHARACTERISTICS OF LIVE BIRTH

	Premenopausal women					
	Age at first live birth (years)					
	≤25 years			>25 years		
	Case/ctrl	OR[1,2]	(95% CI)	Case/ctrl	OR[1,2]	(95% CI)
Number of abortions						
0	49/61	1.0	(reference)	234/231	1.0	(reference)
1	94/92	1.3	(0.8–2.2)	310/302	1.0	(0.8–1.3)
2	61/76	1.0	(0.6–1.6)	109/139	0.8	(0.6–1.1)
≥3	14/26	0.5	(0.2–1.1)	32/22	1.4	(0.8–2.5)
Age at first abortion (years)						
<25	48/61	1.0	(reference)	234/231	1.0	(reference)
25–29	56/82	0.9	(0.5–1.6)	17/21	1.0	(0.5–2.0)
30–34	90/92	1.2	(0.7–1.9)	236/258	0.9	(0.7–1.2)
≥35	21/20	1.2	(0.6–2.6)	198/184	1.0	(0.8–1.3)
	Number of live births					
	1			≥2		
	Case/ctrl	OR[1,3]	(95% CI)	Case/ctrl	OR[1,3]	(95% CI)
Number of abortions						
0	253/266	1.0	(reference)	30/26	1.0	(reference)
1	360/358	1.1	(0.8–1.3)	44/36	1.2	(0.6–2.5)
2	130/180	0.7	(0.6–1.0)	40/35	1.2	(0.6–2.4)
≥3	39/39	1.0	(0.6–1.6)	7/9	0.6	(0.2–2.0)
	Postmenopausal women					
	Age at first live birth (years)					
	≤25 years			>25 years		
	Case/ctrl	OR[1,2]	(95% CI)	Case/ctrl	OR[1,2]	(95% CI)
Number of abortions						
0	114/142	1.0	(reference)	74/67	1.0	(reference)
1	88/125	0.9	(0.6–1.3)	64/81	0.7	(0.5–1.2)
2	59/70	1.0	(0.6–1.5)	41/27	1.3	(0.7–2.4)
≥3	23/19	1.4	(0.7–2.9)	15/12	1.1	(0.5–2.7)
Age at first abortion (years)						
<25	114/142	1.0	(reference)	74/67	1.0	(reference)
25–29	53/64	0.9	(0.6–1.5)	2/1	1.8	(0.1–23.9)
30–34	79/97	1.0	(0.7–1.5)	45/49	0.8	(0.5–1.4)
≥35	38/52	1.0	(0.6–1.6)	73/70	1.0	(0.6–1.6)
	Number of live births					
	1			≥2		
	Case/ctrl	OR[1,3]	(95% CI)	Case/ctrl	OR[1,3]	(95% CI)
Number of abortions						
0	54/38	1.0	(reference)	134/171	1.0	(reference)
1	49/61	0.5	(0.3–1.0)	103/145	1.0	(0.7–1.3)
2	17/24	0.5	(0.2–1.1)	83/73	1.4	(0.9–2.0)
≥3	8/7	0.8	(0.2–2.4)	30/24	1.8	(1.0–3.2)

[1]Adjusted for age, education, family history of breast cancer in first-degree relative, history of fibroadenoma, age at menarche, age at menopause, waist-to-hip ratio, physical activity, duration of breastfeeding, and spontaneous abortion.–[2]Additionally adjusted for number of live births.–[3]Additionally adjusted for age at first live birth.

births had a borderline increased risk of breast cancer (OR = 1.8, 95% CI 1.0–3.2), however the confidence interval surrounding this point estimate is quite wide. The combination of age at first induced abortion and age at first live birth did not influence breast cancer risk.

Table IV presents the induced abortion and breast cancer relation stratified by menopausal status and lactation history. The percentages of women who breast-fed were slightly lower among premenopausal women (75% of cases, 73% of controls) than among postmenopausal women (85% of cases, 92% of controls). Lactation history had little effect on the induced abortion and breast cancer association among premenopausal women. Among postmenopausal women who had an induced abortion after their first live birth and had never breast-fed there seemed to be a reduced risk of breast cancer (OR = 0.3, 95% CI 0.1–0.8). Postmenopausal women who did breast-feed were not at reduced risk of breast cancer.

The spontaneous abortion and breast cancer association is presented in Table V for comparison with the induced abortion and breast cancer relations. Much smaller percentages of women had spontaneous abortions than had induced abortions (premenopausal: 9% of cases, 8% of controls; postmenopausal: 14% of cases, 17% of controls). There was no overall effect of spontaneous abortion on breast cancer risk (OR = 0.9, 95% CI 0.7–1.2). There was a suggestive decreasing risk with increasing number of spontaneous abortions among postmenopausal women (trend test $p = 0.08$). Premenopausal women were at increasing risk of breast cancer associated with increasing age at first spontaneous abortion (trend test $p = 0.04$). Although not significant, the effect of increasing interval between first spontaneous abortion and reference date seemed to be associated with decreasing breast cancer risk among premenopausal (trend test $p = 0.07$) and postmenopausal women (trend test $p = 0.10$). Gestational length of first spontaneous abortion was not associated with breast cancer risk.

TABLE IV – ODDS RATIOS OF BREAST CANCER ASSOCIATED WITH INDUCED ABORTION BY LACTATION HISTORY

Lactation	Induced abortion	Case	Control	OR[1]	(95% CI)
Premenopausal women					
Never	No abortion	78	87	1.0	(reference)
	Yes, before first live birth	29	26	1.4	(0.8–2.6)
	Yes, after first live birth	121	144	0.9	(0.6–1.3)
Ever	No abortion	205	205	1.0	(reference)
	First abortion before first live birth	45	60	0.8	(0.5–1.3)
	First abortion ≤2 years before live birth	21	21	1.3	(0.7–2.5)
	First abortion >2 years before live birth	24	39	0.7	(0.4–1.2)
	First abortion after first live birth	425	428	1.0	(0.8–1.3)
	First abortion ≤2 years after live birth	275	287	1.0	(0.7–1.3)
	First abortion 2–5 years after live birth	97	82	1.1	(0.8–1.6)
	First abortion >5 years after live birth	53	58	0.8	(0.5–1.2)
Postmenopausal women					
Never	No abortion	36	10	1.0	(reference)
	Yes, before first live birth	5	4	0.2	(0.04–1.2)
	Yes, after first live birth	33	29	0.3	(0.1–0.8)
Ever	No abortion	152	199	1.0	(reference)
	First abortion before first live birth	6	10	0.9	(0.3–2.8)
	First abortion ≤2 years before live birth	1	0	—	
	First abortion >2 years before live birth	5	10	0.7	(0.2–2.1)
	First abortion after first live birth	247	291	1.1	(0.8–1.4)
	First abortion ≤2 years after live birth	82	90	1.2	(0.8–1.7)
	First abortion 2–5 years after live birth	81	86	1.2	(0.8–1.7)
	First abortion >5 years after live birth	85	115	1.0	(0.7–1.4)

[1]Adjusted for age, education, family history of breast cancer in first-degree relative, history of fibroadenoma, age at menarche, age at menopause, waist-to-hip ratio, physical activity, spontaneous abortion, age at first live birth, and number of live births.

TABLE V – ODDS RATIOS OF BREAST CANCER ASSOCIATED WITH SPONTANEOUS ABORTION

	Premenopausal women			Postmenopausal women		
	Case/ctrl	OR[1]	(95% CI)	Case/ctrl	OR[1]	(95% CI)
Abortion						
Never	818/872	1.0	(reference)	411/451	1.0	(reference)
Ever	85/77	1.1	(0.8–1.6)	67/92	0.8	(0.5–1.1)
Number of abortions						
1	69/70	1.0	(0.7–1.5)	59/77	0.8	(0.6–1.2)
≥2	16/7	2.2	(0.9–5.5)	8/15	0.5	(0.2–1.3)
		$p = 0.24$			$p = 0.08$	
Age at first abortion (years)						
<25	9/12	0.8	(0.3–2.0)	23/36	0.7	(0.4–1.2)
25–29	51/52	1.0	(0.7–1.6)	26/35	0.8	(0.4–1.3)
30–34	19/13 [2]	1.7	(0.9–3.5)	15/17	0.9	(0.4–1.8)
≥35	6/0 [2]			3/4	0.8	(0.2–3.9)
		$p = 0.04$			$p = 0.51$	
Time of first abortion						
Before first live birth	70/68	1.1	(0.8–1.5)	28/36	0.8	(0.4–1.3)
After first live birth	15/9	1.6	(0.7–3.7)	39/56	0.8	(0.5–1.2)
Number of abortions relative to first live birth						
Before first live birth						
1	57/61	1.0	(0.7–1.4)	26/33	0.8	(0.4–1.3)
≥2	13/7	1.9	(0.7–4.8)	2/3	0.7	(0.1–4.1)
		$p = 0.65$			$p = 0.91$	
Interval between first abortion and reference date (years)						
0–9	10/11	1.4	(0.6–3.4)	1/0 [2]		
10–14	30/23	1.5	(0.9–2.7)	2/2 [2]	2.2	(0.4–14.0)
15–19	24/23	1.0	(0.6–1.9)	3/2	1.3	(0.2–8.0)
≥20	21/20	0.8	(0.4–1.5)	61/88	0.7	(0.5–1.0)
		$p = 0.07$			$p = 0.10$	
Gestational length of first abortion (weeks)						
1–8	46/35	1.3	(0.8–2.1)	28/37	0.8	(0.5–1.3)
9–12	26/29	1.0	(0.6–1.7)	21/38	0.6	(0.3–1.0)
≥13	13/13	0.9	(0.4–2.1)	16/17	1.0	(0.5–2.0)
		$p = 0.46$			$p = 0.17$	

[1]Adjusted for age, education, family history of breast cancer in first-degree relative, history of fibroadenoma, age at menopause, waist-to-hip ratio, physical activity, duration of breastfeeding, induced abortion, age at first live birth, and number of live births.–[2] Categories collapsed to calculate OR.

DISCUSSION

Our overall null association for breast cancer as it relates to induced abortion is in agreement with several recent case-control studies conducted among women of all age groups,[9–11] and restricted to younger women.[12–14] We are also in agreement with 2 recent cohort studies that reported relative risks of 1.0 (95% CI 0.94–1.06)[15] and 1.1 (95% CI 0.8–1.6),[2] respectively. Nor did we find an increased risk associated with several induced abortions. We compared our results with studies con-

ducted in countries where induced abortions are common, Russia, China and Japan. Our results are similar to 2 case-control studies,[16,17] but differ from 3 case-control studies that found elevated breast cancer risks associated with ever having had an induced abortion and with increasing number of induced abortions.[18–20] The studies that reported positive associations between induced abortion and breast cancer risk may have been limited by their failure to control for age at first birth,[18,20] or by their use of hospital-based cases and neighborhood controls.[19]

The 1 previous study of this association conducted in China has only appeared in abstract form.[19] Bu *et al.*[19] reported an elevated risk of early breast cancer among parous women who had an induced abortion (OR = 2.9, 95% CI 1.9–4.4), which was more pronounced among women who had 2 or more induced abortions (OR = 3.6, 95% CI 2.2–6.0). This increased risk is surprising because the majority of women in China have several induced abortions after a first live birth,[21] which is known to be protective against breast cancer.[7,22,23] The extremely high odds ratios reported for known breast cancer risk factors such as age at first birth older than 30 years (OR = 7.8, 95% CI 3.2–19.0) and family history of breast cancer (OR = 9.0, 95% CI 2.6–31.5) found in this study also raised concerns about the methodology used in this study.

The most common early abortion procedure used in China during the childbearing years of the majority of the women in the study was vacuum aspiration.[24] For women undergoing late abortions, intra-amniotic injections of abortifacients like rivanol or Traditional Chinese yuanhuacine were used.[25] After late abortions, a number of methods have been used to inhibit lactation including hormones, such as diethylstilbestrol (DES), dopamine agonists, and breast compression.[26] Because fewer than 5% of women in the present study had induced abortions after the first trimester, and the most common practice in China is to use Traditional Chinese topical ointments for lactation inhibition, it is unlikely that the use of hormones to inhibit lactation had much of an impact on breast cancer risk.

The biological mechanism that has been proposed to explain the increased risk of breast cancer associated with induced abortion in some studies pertains to the undifferentiated nature of breast cells during the first trimester of pregnancy among women without a full-term pregnancy.[27] In animal studies, Russo *et al.*[28] found that the breast tissue of rats whose pregnancy was terminated early began to proliferate, but did not differentiate as is done during a full-term pregnancy. These undifferentiated cells may become vulnerable to malignancy. Presumably, the greater number of induced abortions that occur before a full-term pregnancy the greater number of undifferentiated breast cells at risk of malignancy. This may help explain the elevated breast cancer risk with increasing number of abortions reported in Russia[18] and Japan,[20] because women in those countries tend to have several abortions before a first live birth. We, however, found no difference between first induced abortion occurring before or after the first live birth, in agreement with most studies of this topic,[11,29,30] although only a few women reported they had an abortion before the first live birth in our study population.

This study has many strengths. The population-based nature of the study and its extremely high response rates (cases: 91%; controls: 90%) minimizes selection bias. Underreporting of induced abortions is unlikely in our study given its' widespread use in China as a family planning method in case of contraceptive nonuse or failure.[21] China has had a series of family planning campaigns in place since 1956. Induced abortion was legalized in China in 1957 around the time most of the women in this study were beginning their childbearing years.[6] The procedure is free of charge and readily available. Because the primary method of family planning in China at the time most women in this study were using contraception was the intrauterine device that was known to have high failure rates and women were expected to have a child soon after marriage, women oftentimes had more than 1 abortion after the birth of their first or second child but not before their first live birth. Because of this and because Chinese women who have several induced abortions do not feel stigmatized, we believe that the information on abortion collected in our study is rather accurate. Our notion is supported by the findings of 3 recent studies of induced abortion in Shanghai,[31] Beijing[32] and 4 northern counties in China[33] that reported percentages of women with a history of induced abortion of approximately 60%, similar to the percentage seen in this study.

We adjusted for known breast cancer risk factors and evaluated the induced abortion-breast cancer association in conjunction with first live birth, lactation and number of pregnancies. Past studies of the induced abortion and breast cancer association have been limited by combining induced and spontaneous abortions, choosing an inappropriate reference group, failing to control for effect modification and confounding, and suspected underreporting of induced abortions among controls.[34,35] We analyzed induced and spontaneous abortions separately, and adjusted for the other outcome in the analysis. Because of the low rate of nulliparity and extremely low induced abortion rate among nulliparous women, our analysis was restricted to parous women, which prevented us from assessing whether the induced abortion and breast cancer relation was stronger among nulliparous than among parous women. The effect of some hormonal exposures on breast cancer risk is thought to differ by menopausal status,[36] therefore we presented our results separately by menopausal status even though there was no evidence of effect modification. In this low-risk country, only 54 cases and 38 controls had a first-degree family history of breast cancer preventing us from assessing its' role as an effect modifier.

In summary, our study indicates that a history of several induced abortions has little influence on breast cancer risk in Chinese women. Although we obtained relevant information regarding multiple induced abortions before a first live birth, we were unable to evaluate its effect on breast cancer risk due to the extremely low frequency in this population (<2% of women who had induced abortions). Nor were we able to adequately investigate the effect of induced abortion at a very young age. Future studies should assess these relations to clarify the role that induced abortion may play in breast cancer risk.

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